

Editorials

Coalitions Make Sense

THE GROWING INTEREST within organized medicine to achieve some of its goals by working through coalitions of groups and organizations that share these goals makes eminent sense. For some time it has been increasingly clear that the medical profession, standing alone, simply does not have the social, economic or political muscle to bring about some of the changes that it believes are necessary in the patients' and public interest. Our real strength lies in our understanding of the science and technology of patient care, in our usually unflinching advocacy of what we believe best for patients and in our intimate participation in caring for those who are sick, injured or emotionally disturbed and also in the more generic problems of health care. So far we have not been as successful as we could wish in bringing these real strengths to bear in the social, economic and political arenas of health care as these exist today. The battles are being fought on turf other than our own and often under rules that seem not to speak to what we know to be the realities of health care, at least as physicians and many patients understand them.

As our overall society has become more complex and costly (this due to technologic progress, increasing specialization and interdependence between men and machines and the need for some formal organization and often bureaucratic governance to make it work), health care has surfaced as the most visible focus of many problems that will inevitably develop in other segments of an increasingly complex society. Problems such as equity, justice, access, costs, quality and inability to provide everything we know how to provide for everyone who has a legitimate need will not for long be confined to the field of health care. Similar kinds of problems are clearly on the horizon in our legal system, our educational system and even in much of business and industry. In health care, at least, these are not due to poor performance. Rather they are problems of unprecedented success.

But to focus more closely on the role of the medical profession in health care, we have many of these new kinds of problems in spades. Neither our democratic profession nor our democratic society has yet learned how to deal with them. In some ways society seems to be looking to the profession for leadership and in other ways it seems to be doing everything it can to weaken the profession, if not to render it impotent. Nevertheless, everyone seems to be groping for solutions. This kind of situation cries out for leadership, whether in the public or private sector, and in a democratic system leadership cries out for support, for allies, if it is to succeed.

The issue of tort reform is a case in point. The problem surfaced seriously first in health care, in the sudden unavailability of professional liability insurance for physicians, and this was so severe that in 1975 the California Legislature enacted the Medical Injury Compensation Reform Act (MICRA) which among other things placed limits on noneconomic awards and attorneys' contingency fees. Ten years later, in 1985, this pioneering California law was upheld by the United States Supreme Court, and for the first time the law

became fully operative. As might be expected, those who oppose this law are now seeking to challenge it both in the Legislature and at the ballot box. All of this accomplishment was spearheaded by the California Medical Association, but it was not done without allies. A coalition with other groups having similar concerns contributed substantially and essentially to this success.

But the broader liability problem, of which the medical professional liability had surfaced as the tip of an iceberg, was not solved. Public liability insurance of all kinds became progressively less available, and has provided progressively less coverage for insureds over the last decade. Another coalition, again strongly supported by the California Medical Association, has now addressed this broader problem and has placed a Taxpayers for Fair Responsibility "deep pocket" initiative on the California ballot. This proposition addresses the problem of joint and several liability by limiting any one defendant's financial responsibility for the pain and suffering portion of the award to the actual percentage of legal fault. It is gaining strong public support, far beyond what could have been mobilized just within the health care enterprise, and will be voted on by Californians as Proposition 51 on June 3.

All of this seems to show that health care is at the cutting edge of many of the social, economic and political problems of our evolving and increasingly interdependent and costly complex society. It has also shown that the medical profession and organized medicine simply do not have the strength to go it alone in these social, economic and political arenas, but that they can be an effective stimulus or focal point to involve others with similar interests and similar problems to work cooperatively to help solve a common problem. Properly chosen and properly structured, such coalitions not only can be very effective, they make sense.

MSMW

Paraneoplastic Syndromes

THE PARANEOPLASTIC SYNDROMES are a diverse group of clinical disorders associated with cancer which can involve nearly every organ system. These syndromes of various symptoms, signs and laboratory abnormalities occur at a distance from the primary tumor and are not produced by invasion and growth of metastasis. All of these syndromes as a group have also been referred to as the remote effects of neoplastic disease and have been the subject of several excellent reviews.¹⁻⁴

Many paraneoplastic syndromes have been recognized for years, and the list continues to change and grow as we improve our ability to differentiate these syndromes from other unrelated conditions, improve our understanding of their etiology and pathogenesis and improve the sensitivity of techniques to measure organ dysfunction. Many neoplasms, it is increasingly recognized, secrete or release a variety of substances—hormone precursor molecules, hormones, hormone fragments, hormonelike products, fetal proteins, enzymes and other proteins—into the circulation. Except for a few

instances, these substances are not associated with clinical abnormalities, or an association is not yet appreciated.

Paraneoplastic syndromes are not rare and occur with many types of neoplasms. Certain neoplastic diseases, however, such as small cell lung cancer, carcinoid tumors, squamous cell lung cancer, promyelocytic leukemia, prostatic carcinoma, renal cell carcinoma, hepatoma, thymoma and others are quite commonly associated with distinct syndromes. It has been difficult to determine the frequency of paraneoplastic phenomena for a number of reasons. Systematic prospective case-control clinical evaluations with special attention to characterizing these syndromes are lacking. In addition, there have been problems with uniformly defining these syndromes, particularly in view of several confounding clinical variables and the obscure cause of most of these remote effects.

The etiology and pathogenesis of the majority of the paraneoplastic syndromes remain unknown. Perhaps the best understood syndromes are those which are produced by neoplasms that secrete hormones or hormonelike substances, including, for example, adrenocorticotrophic hormone (ACTH), antidiuretic hormone, parathyroid hormone and human chorionic gonadotropin. The course of the clinical syndrome associated with secretion of these active hormones closely mirrors the course of the underlying neoplasm. The target organ effects are similar to those seen by excessive production of the same hormones by endocrine glands. Effective treatment of the neoplasm also treats the syndrome by stopping the production and secretion of the hormone. Several syndromes have been identified with different neoplasms. A few examples are Cushing's syndrome (small cell lung cancer, bronchial carcinoids and others), the syndrome of inappropriate secretion of antidiuretic hormone (small cell lung cancer and others), hypercalcemia from elevated parathyroid hormone (squamous cell lung cancer, renal cell carcinoma and others) and gynecomastia from elevated gonadotropin (germ cell neoplasms, gastric carcinoma and others). As mentioned, a large variety of circulating substances are also being identified by radioimmunoassay and as yet have not been associated with any known clinical abnormalities. It is likely, with further study, that current syndromes of unknown cause or new syndromes will be attributed to these or other tumor-related substances.

Other than the few examples of documented hormone production by neoplasms and the clinical findings from target organ effects, the etiology and pathogenesis of the majority of the other syndromes which manifest in nearly every organ system remain unknown. Circumstantial evidence has led to speculation concerning the cause of many of these clinical abnormalities. Some of these theories include autoimmune and immune complex, infectious agents, production of biologically active substances (hormones, enzymes, immunoglobulins, other proteins) which can either block a normal receptor function and inhibit a normal function or inappropriately act without homeostatic control. Some of the "paraneoplastic" syndromes will be found to have a cause not directly related to the neoplasm. Progressive multifocal leukoencephalopathy was felt to be paraneoplastic in the past, but a viral cause was later established.⁵

Further characterization and understanding of the paraneoplastic syndromes are important for several reasons. At times the syndrome is the major clinical problem requiring

attention, and appropriate palliative management may be important for the quality and duration of patient survival. Depending on the circumstances, the best overall management plan might be symptomatic control of paraneoplastic symptoms and signs. Treatment of hypercalcemia in patients with metastatic squamous cell carcinoma of the lung or renal cell carcinoma is an example. The treatment of metabolic abnormalities can often be a more effective palliative maneuver than attempts to deal with some underlying advanced neoplasms.

Signs, symptoms and laboratory abnormalities associated with paraneoplastic syndromes may be the first clue of an underlying neoplasm, allowing for early detection, perhaps in a more treatable state. Conversely, recognition of paraneoplastic effects as separate from metastatic disease will not delay timely, effective, local treatment in a patient who otherwise may be felt to have metastatic neoplasm. Careful differentiation of paraneoplastic effects from other problems such as infection; fluid and electrolyte disorders; chronic cardiac, pulmonary, renal or hepatic diseases; collagen vascular diseases, and metastatic disease is important in planning appropriate management.

In some instances, and I hope more often in the future, tumor products such as hormones, hormonelike substances, enzymes or other peptides can be used as markers for neoplastic disease activity to detect early recurrence or to help plan further treatment. Hormones or hormonelike products secreted by tumors may be required for continued growth of the neoplasm. Growth factors necessary for continued growth have been demonstrated in tissue culture systems⁶⁻⁸ and, if operative in vivo, may provide a potential avenue for blocking this growth factor effect.

Finally, the opportunity to study hormones and hormone-like substances produced by neoplasms has led to a better understanding of the physiology and biochemistry of normal hormones. The precursor or prohormone molecule of ACTH (pro-opiomelanocortin) and its related fragments have, in part, been characterized and further studied by hormone production in vivo and in vitro from human neoplasms.^{9,10} A better understanding of the protean remote effects produced by neoplasms may provide insight into other basic mechanisms and help to further our understanding of normal physiology and to help solve some of the biologic riddles of neoplastic growth.

A feature which highly suggests that an associated syndrome is produced in some fashion by a neoplasm is the observation of improvement or resolution of the signs, symptoms or laboratory abnormalities of the syndrome after effective treatment of the underlying neoplasm. With a few exceptions, there have been no comprehensive case-control studies looking at any specific syndrome and its relationship to therapy for the neoplasm. Most of these data are in the form of isolated patient reports and small groups of patients.

Dr Markman in this issue has written an informative review of the response of paraneoplastic syndromes to antineoplastic therapy. He discusses the limitations of this type of retrospective literature search, particularly of the heterogeneous group of paraneoplastic syndromes which are often difficult to accurately define and, at times, to separate from the space-occupying effects of neoplastic disease, other underlying illnesses or drug toxicities. His review highlights the

reported response to therapy of the syndromes in many organ systems. Some of the syndromes, such as neurologic dysfunction, have been documented to resolve in only a small number of patients and may be explained by the relatively ineffective therapy for the neoplasm, irreversible damage to cells, tissues and organs (such as the central nervous system) or an independent or unrelated cause and pathogenesis for the syndrome.

Documented reduction or resolution of paraneoplastic effects has followed resection of several types of neoplasms. Unfortunately, many paraneoplastic syndromes are more often recognized with advanced metastatic neoplasms, many of which are currently ineffectively treated. As therapy improves, particularly for metastatic neoplasms, we are likely to observe alleviation in many of the associated syndromes after administration of effective antineoplastic therapy. In the past 15 years, curative chemotherapy has been developed for a portion of patients with several metastatic neoplasms: acute lymphocytic leukemia, choriocarcinoma, Hodgkin's disease, diffuse high-grade non-Hodgkin's lymphoma, testicular carcinoma and other germ cell neoplasms, ovarian carcinoma, acute myelogenous leukemia, Wilms' tumor, embryonal rhabdomyosarcoma, Ewing's sarcoma and small cell lung cancer. In addition, patients with several other advanced cancers—breast carcinoma, low-grade indolent non-Hodgkin's lymphoma, chronic leukemia and many others—respond favorably to chemotherapy and, although not cured, enjoy an improved survival. The paraneoplastic syndromes associated with these neoplasms are likely to improve or resolve with antineoplastic therapy, but this clinical question has not usually received emphasis in most reports. There are several well-known and accepted examples, however, of remarkable reduction in paraneoplastic phenomena with effective combination chemotherapy. The "B symptoms" (fever, weight loss, night sweats) and pruritus with Hodgkin's disease and non-Hodgkin's lymphoma regularly resolve following chemotherapy and remission of the tumor. The majority of patients with Hodgkin's disease and diffuse high-grade non-Hodgkin's lymphoma are now cured. Gynecomastia is seen in some men with germ cell tumors, particularly those with choriocarcinoma elements and elevated plasma human chorionic gonadotropin levels. The hormone level drops and gynecomastia usually resolves after effective combination chemotherapy for the germ cell tumor. Most of these patients are also cured. The hyponatremia of the syndrome of inappropriate antidiuretic hormone secretion seen in approximately 10% of patients with small cell lung cancer at diagnosis usually resolves within three to six weeks after combination chemotherapy, but often recurs with tumor relapse. A few of these patients are also cured of their neoplasm. Before effective antineoplastic therapy was developed, these groups of patients continued to suffer from the neoplastic growth and the paraneoplastic effects. In the future, with newer and more effective approaches to the therapy for many neoplasms, the hope is that paraneoplastic syndromes will become less important as clinical problems.

F. ANTHONY GRECO, MD
Professor of Medicine
Director, Medical Oncology
Vanderbilt University School of Medicine
Nashville, Tennessee

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'The Care and Well-being of Patients'

WHEN ONE THINKS about it, it is surprising that the formally stated purposes of most medical associations make no mention of the care and well-being of patients. This has been true of the California Medical Association, it is true of the American Medical Association and we suspect it is true of most of the associations that comprise what we know as organized medicine. No doubt the care and well-being of patients has always been taken for granted by those within and without the profession. But this may no longer always be the case. It has come to pass that there are those who believe that medical associations are first and foremost physicians' protective associations.

And so if someone, perhaps a young newspaper reporter about to write a story, were to go to a public library and look up the stated purposes of a medical association, what would he or she find? In the case of the California Medical Association, the purposes until recently were "to promote the science and art of medicine, the protection of the public health, and the betterment of the medical profession." There was not a word about patients or patient care, which is what many in the profession believe we are all about.

Upon recommendation of a committee on long-range planning, the 1986 House of Delegates of the California Medical Association changed the purposes in the association's constitution to read "to promote the science and art of medicine, *the care and well-being of patients*, the protection of the public health, and the betterment of the medical profession."

In this writer's view, the newly worded statement not only gives public expression to a purpose that has been there all the time, but also places the series of organizational commitments in the proper sequence of their relative importance. We hope that other organizations within organized medicine will soon place "the care and well-being of patients" high on their masthead for all to see, and in doing so legitimize organizationally the role of patient advocacy now being espoused by the leadership of our profession.

MSMW

Typhoid Fever—'Recherches du Temps Perdu'

FROM TIME TO TIME we see on our wards a patient with a classic disease, one which reminds us of times past in our own medical history. In the case of typhoid fever, the disease not